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TRENCH FOOT AND IMMERSION FOOT*

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FROSTBITE and kindred injuries to the feet from cold have been recorded as a source of casualties in military campaigns since the epic retreat of the Greeks under Xenophon across the snow-covered mountains of Armenia. Cold does not necessarily produce a single type of injury, as many have supposed, but may result in several distinct syndromes, which become of particular importance in time of war, when clothing, food, heat and shelter are likely to be inadequate and great numbers of indoor dwellers are exposed to the rigors of outdoor life. These clinical and pathologic changes have been summarized by Greene,[1] who has had an unusual opportunity to study them. Wet cold is far more difficult to deal with than are severer degrees of dry frost, as was found by Larrey[2] in the retreat of the Napoleonic armies from Moscow and by the medical officers on duty with the American troops who landed on Attu.

The two conditions to be considered herein, trench foot and its seagoing counterpart, immersion foot, are both caused by prolonged exposure of the dependent lower extremities to cold and moisture. The knowledge of trench foot as it is occurring during the present war is based largely on information acquired from Army surgeons who have taken care of many of the Aleutian casualties, in particular from Colonel R. H. Patterson and Major F. M. Anderson, of the Letterman General Hospital, and from Captain A. Lesser, with whom one of us (W.B.S.) was formerly associated at the McCaw General Hospital. Recently Captain M. H. Harris and Major G. L. Maltby,[3] of Ashford General Hospital, have presented a series of 130 cases resulting from the Italian campaign. These officers have been kind enough to contribute valuable criticism and advice, as well as to permit us to use much of their data for the compiling of this report. Since the writing of this article the War Department[4] has issued a comprehensive digest on trench foot.

Our information on immersion foot has been acquired largely through personal experience with survivors of torpedoed vessels who have been exposed to cold water during a prolonged period adrift in the North Atlantic.[5] The opportunity to examine a large number of these men was obtained through the kindness of Surgeon Commander D. R. Webster, Surgeon Lieutenant F. M. Woolhouse and Surgeon Lieutenant J. L. Johnston, of the Royal Canadian Navy. Others have been examined at the Columbia-Presbyterian Medical Center in New York through the courtesy of Dr. David C. Bull and at the Massachusetts General Hospital, in addition to those cared for at the United States Naval Hospital in Chelsea.

PATHOLOGIC PHYSIOLOGY

In a crowded lifeboat or Carley raft the survivors are forced to sit with their wet feet dependent and immobile. This alone is sufficient to produce edema, and if starvation is an added factor, so that the plasma proteins are reduced, the edema becomes pronounced even in the absence of cold. No lifeboat or raft is dry, and boots are not issued that will keep the feet both dry and warm. Occasionally when a man has been forced to kneel for prolonged periods on the floorboards of a wet boat or to sit on the bottom of a rubber raft, the same condition has involved the knees or the buttocks.

In the landings in the Aleutians men were forced to take cover in foxholes in a semisitting position for periods ranging from three to fourteen days, in melting snow by day and in light frosts at night. During this period they had little to eat, were thoroughly chilled and had no opportunity to change their footgear. No leather boots can keep out the wet under these conditions, and even rubber ones become moist on the inside from perspiration. Under these circumstances all the factors that damage the tissues in a crowded lifeboat in the North Atlantic are present ashore — exposure of the legs to cold just above freezing, wetness, dependency and immobility, and general chilling of the body.

Immersion foot and trench foot differ from frostbite simply because the tissues are not actually

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frozen. Ice crystals do not form in living tissue above the freezing point of sea water or of mud and thawing snow, but at temperatures from this point to above 50°F. the feet gradually become chilled,

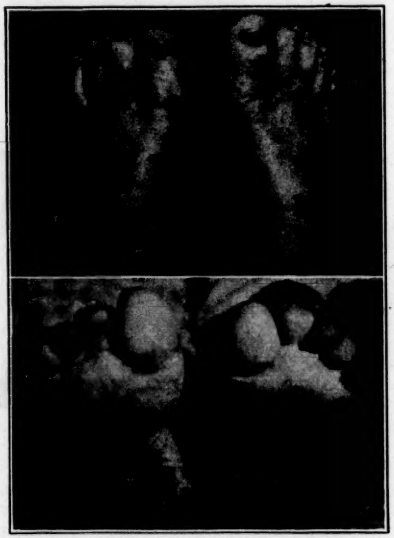

FIGURE 1. *A Case of Immersion Foot.*

These photographs were taken of a patient of Surgeon Commander Webster, R.C.N.M.C., on the twelfth day after rescue. The man had been in a lifeboat without shoes for four days in the North Atlantic in March. The temperature of the sea water was recorded at 34°F., and his feet had been wet most of the time. The petechial hemorrhages and subcutaneous swelling are well shown. Blisters were present, but shrank following cooling to 70°F. with ice bags. There was threatened gangrene of the third and fifth toes on the left and the second, third, and fifth toes on the right, which eventually necessitated local amputation of several after infection, which entered through areas of epidermophytosis.

numb and swollen (Lewis[6]). Lesions resembling trench foot have been reproduced in rabbits by shaving the legs and keeping the animals standing for a number of days in a refrigerated chamber on wet mud at a few degrees above freezing (Smith, Ritchie and Dawson[7]). Tissue changes similar to those seen in immersion foot have recently been produced experimentally by Blackwood and Russell[8] in the tails of rats by keeping the floors of the cages wet with sea water at 40°F. for periods of two to four days. In sailors adrift at sea these changes may begin in the course of a few hours, but in the trenches, where the feet get wet and chilled more slowly, an exposure of several days is necessary. The condition at sea differs from that seen in troops campaigning in slush and cold mud simply because men in a crowded lifeboat do not have the opportunity to walk and thus to traumatize their anesthetic feet. When this occurs, infection is likely to follow and to end in moist gangrene. After the recent campaign in the Aleutians, 6 cases of a total of 231 treated by Patterson and Anderson[9] required amputation of one or both feet, and 18 other patients lost the greater part of one or more toes. At the McCaw General Hospital, 21 of 35 severe cases from Attu required late plastic amputation revisions of toes or distal portions of the feet by Captain Lesser.

After exposure at sea, infection and gangrene are fortunately less frequent than is the case on land. In approximately 100 cases that we have seen, only 1 man lost his leg, — after exposure for a prolonged period adrift in bitter cold off the northern tip of Norway in January, — and 2 others suffered the loss of one or more toes. After comparing our observations of trench foot with those of immersion foot,

FIGURE 2. *A Severe Case of Trench Foot from Attu.*

In this case, amputation of both feet was eventually necessary because of the depth of tissue necrosis and because gas bacilli were found on smear and culture. (Reproduced by courtesy of Col. R. H. Patterson and Maj. F. M. Anderson, M.C., A.U.S., Letterman General Hospital.)

it is our impression that the former causes more extensive and severe damage to the tissues than does the latter.

When first seen after exposure, either ashore or afloat, the feet are cadaveric in color, swollen and

blistered (Fig. 1). Massive gangrene from the ankle down may appear imminent (Fig. 2), but in the absence of infection and with proper treatment the capacity for recovery is amazing. It takes place in two stages, an early hyperemic stage and a later period of fibrosis. If the exposure has been severe and prolonged, pain may be severe in both and may cause prolonged incapacity.

The hyperemic phase develops as soon as the legs become warm and circulation recovers. This vasodilator response is a sterile inflammatory reaction blistering, as well as the late fibrosis (Drinker and Field[11]). The combination of heat, which raises the metabolic demands of the cells for oxygen, and of an inadequate superficial circulation results in cutaneous anoxia and burning pain as soon as the nerves recover (White[5]). Recovery of sensation takes place rapidly over the proximal parts of the feet, but in the severer cases the toes may remain anesthetic for weeks.

In the course of one to four weeks the hyperemia subsides and the circulation returns to normal.

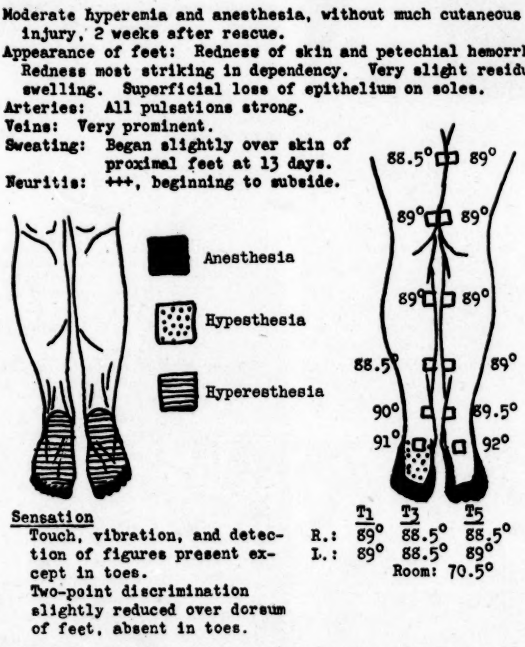
Moderate hyperemia and anesthesia, without much cutaneous injury, 2 weeks after rescue.
Appearance of feet: Redness of skin and petechial hemorrhages. Redness most striking in dependency. Very slight residual swelling. Superficial loss of epithelium on soles.
Arteries: All pulsations strong.
Veins: Very prominent.
Sweating: Began slightly over skin of proximal feet at 13 days.
Neuritis: +++, beginning to subside.
Anesthesia
Hypesthesia
Hyperesthesia
88.5° 89°
89° 89°
89° 89°
88.5° 89°
90° 89.5°
91° 92°
Sensation
Touch, vibration, and detection of figures present except in toes.
Two-point discrimination slightly reduced over dorsum of feet, absent in toes.
T1 T3 T5
R.: 89° 88.5° 88.5°
L.: 89° 88.5° 89°
Room: 70.5°

FIGURE 3. *Sensory Changes and Surface Temperatures in a Case of Immersion Foot.*

caused by the absorption of damaged tissue. There are bounding pulsations in the deep vessels, and heat, radiating to the surface, makes the skin feverhot (Fig. 3). In addition, the circulation of the superficial tissues, which have been more thoroughly penetrated by the cold, may be profoundly impaired. Evidences of this are the petechial hemorrhages caused by ruptured capillaries and the thrombosis of the subcutaneous blood vessels (described by Patterson[10]). Capillary permeability is greatly increased, resulting in the extravasation of protein-rich fluid that cannot be removed by the injured lymphatics. This accounts for the gross edema and The blebs absorb and the skin peels off with a certain amount of scarring. The patients with milder cases are then fit to return to duty, but in those with severer damage the skin is atrophic (Fig. 4), movement of the toes is limited (Fig. 5), and walking is made difficult by pain. No satisfactory explanation for the rigid, weak feet and pain on walking had been given until the past winter. Dr. Shields Warren and one of us (J.C.W.)[12] examined a series of biopsies of skin and superficial muscle from the feet of 6 men who were still incapacitated several months after their exposure. These biopsies showed atrophy and thinning of the epidermis, with intense fibrosis and

deposition of collagen around the nerve endings and subcutaneous blood vessels (Fig. 6). The muscles were also infiltrated and their fibrils separated by a network of scar tissue (Fig. 7). The extent of this reaction depends on the initial exudation of fibrin and tissue anoxia. It is the logical explanation for the late pain, rigidity and weakness of the feet, a condition that tends to improve spontaneously in six to eight months, the time at which collagen ceases to contract. In some of the worst cases of immersion foot on record, however, pain has remained troublesome for over two years (Ungley[13]).

FIGURE 4. *A Late Case of Trench Foot After Conservative Local Amputation and Healing.*
This photograph illustrates the cutaneous fibrosis, the severe contractures and the rigidity of the toes. (Reproduced by courtesy of Captain Albert Lesser, McCaw General Hospital.)

that, in addition to the widespread fibrosis, other contributory factors in this prolonged period of disability are the weakness and deformities of the feet secondary to their long-continued immobilization and the hyperesthesia that frequently accompanies the return of sensation after nerve injury in any part of the body.

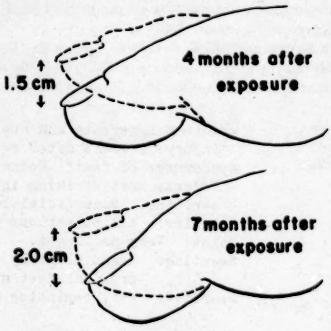

FIGURE 5. *A Late Case of Immersion Foot.*
This photograph illustrates the rigidity and limited movement of the toes. Note the improved mobility after three months of orthopedic exercises and physiotherapy. (Reprinted from White and Warren[12] by permission of the publisher.)

A final point to remember in the pathogenesis of these swollen, painful feet after prolonged periods of cold and wet is the role of malnutrition and avitaminosis. One of us (J.C.W.[14]) has seen extreme swelling, numbness and pain develop after two weeks of dehydration and starvation with exposure in the

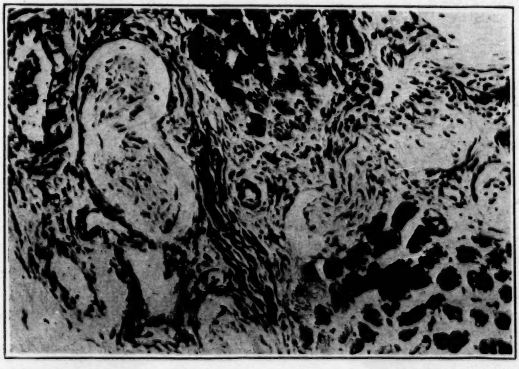

FIGURE 6. *Photomicrograph of a Section of the Extensor Brevis Digitorum Muscle.*
Note the perineural fibrous tissue and the edema of the nerves (x 220; Masson trichrome stain). (Reprinted from White and Warren[12] by permission of the publisher.)

After seven months even the patients with mild cases of trench foot from Attu were for the most part still unable to march on account of hypersensitive feet. Patterson and Anderson[9] have suggested

warm waters of the Gulf Stream. These conditions were caused not by tissue injury from cold but by hypoproteinemia and avitaminosis — particularly through depletion of the vitamin B complex. Similar conditions are even likelier to be found in the starving inhabitants of Europe and Asia.

Treatment

When men with chilled, numb, swollen and blistered lower legs are first seen by a medical officer, they must be kept off their feet and the skin protected against rupture of the blebs and the formation of pressure sores in the weight-bearing areas of anesthetic skin. Once streptococcal infection has begun, moist gangrene and loss of the leg are likely to follow. First aid should therefore be begun by having the patients carried to the sick bay or hospital near the front lines and kept in bed.

Figure 7. *Photomicrograph of a Section of the Extensor Brevis Digitorum Muscle. Note the fibrous tissue about nerves and between the muscle bundles (x 35; phosphotungstic acid-hematoxylin stain). (Reprinted from White and Warren[12] by permission of the publisher.)*

Entirely different forms of treatment are required for the general effects of cold and the local damage from exposure. The body should be warmed externally by covering with blankets and hot-water bottles, and internally by drinking hot soup, coffee or tea. The patients should be given nutritious, easily digested food with a high protein-vitamin content as soon as it can be tolerated. In the sickest survivors, vitality may have been so reduced by cold and starvation that emergency treatment for shock is needed. Transfusion of plasma then plays a double role by restoring depleted fluid volume and combating hypoproteinemia.

It is vitally important to keep the injured feet of the chilled patient cool while the body is warmed. This is best accomplished by exposing the legs below the knees to a cool room temperature and directing a blast of air from an electric fan or blower over them. The feet should never be rubbed or the blistered areas painted with a strong disinfectant. Like a second-degree burn, these areas should be handled with aseptic precautions, including masking of the dresser's nose and mouth, sulfonamide therapy and a "booster dose" of tetanus toxoid. Elevating and cooling the legs helps to drain the edema fluid and causes the blisters to shrink. During the period of sterile inflammation the hyperemia of the deeper tissues, which are always less damaged by cold than is the skin, causes the surface temperature to rise to above 90°F. Unless this excessive heat is reduced, cyanosis increases, blisters swell, and pain becomes acute. The explanation of this is that warming increases the metabolic demand for oxygen on the part of the cutaneous cells to a greater extent than can be met by the impaired supply of blood through the injured subcutaneous vessels. Anoxia therefore ensues, with throbbing pain, increased extravasation of fluid and necrosis of the skin.

After arrival in a naval or Army base hospital the same local treatment should be continued for a week or more, until the hyperemia due to absorption of damaged tissue has subsided and circulation through the thrombosed subcutaneous vascular bed has recovered. The greatest advance in the treatment of the acute hyperemic stage has been the application of continuous cooling by Webster, Woolhouse and Johnston.[15] In general, local cooling should be pushed to the point where pain is relieved. The ideal cutaneous temperature level is between 75 and 70°F. This has been established by Safford and Nathanson[16] both by clinical observation and on theoretical grounds. Cooling lowers the metabolic

need for oxygen to a point at which sufficient quantities can be supplied through the injured capillary bed. When the feet are cooled the appearance of the skin improves, blisters shrink, and pain is relieved. In the severest cases cooling with room air is insufficient and treatment with ice bags may be necessary. When the latter are used, sterile pledgets of cotton are placed between the toes and the whole foot is covered with a sterile towel. Thoroughly dried ice bags are then placed around each foot over the towel, and the whole is encased in an oiled-silk bag, around which in turn are wrapped thick layers of cotton waste or other insulating material. A rubber pillowcase, loosely tied below the knee, forms a satisfactory outer covering. At first, two to four ice bags are necessary to cool the foot to the optimum temperature of 75 to 70°F. Ordinarily it is sufficient to change them every four hours, and at these times the toes should be palpated to make sure that they are not too severely chilled. It may be necessary to carry out this treatment for periods ranging from several days to two weeks, but as hyperemia subsides less ice is required, and finally exposure to cool air alone suffices.

In the rare cases in which edema and blistering are pronounced but pain is so slight that cooling of the skin is not vital, compressive dressings, which are so effective in second-degree burns, deserve a trial. This has been suggested to us by Dr. Sumner L. Koch,[17] but to date no suitable case has been found for trial.

When gangrene has already developed before the patient enters the hospital, periodic débridement and painstaking care of the feet are necessary. In most cases the extremities can be saved, at least in part, by conservative amputation of toes and the distal portions of the feet (Fig. 8). Early amputation of a leg is excusable only in fulminating lymphangitis, threatened septicemia or gas gangrene.

When the products of tissue damage have been absorbed, circulation returns to normal, blebs absorb, and the skin desquamates. In the mildest cases the patients may be fit to return to duty within two weeks, but severe disability may last for months. All severe cases of trench and immersion foot run a prolonged convalescence of six or more months because of interstitial scarring and pain. The scarring results in rigidity and contractures of the toes, as well as atrophy and weakness of the ligaments and intrinsic muscles of the feet. The pain is of two varieties — a burning, hyperesthetic type, probably due to irritation of nerve endings by scar tissue, and a dull ache in the arches and ankle joints, probably due to a combination of muscle weakness, disuse, rigidity and fallen arches. Physiotherapy and orthopedic exercises are helpful in restoring power to the intrinsic muscles and weakened arches, but often fail to give sufficient relief.

A vast saving in man power for the Army, Navy and Merchant Marine can be achieved if a method is found to shorten this period of pain and rigidity. Although sympathectomy is quite illogical in the early hyperemic stage, it is possible that release of vasoconstrictor tone will reduce these late disabling

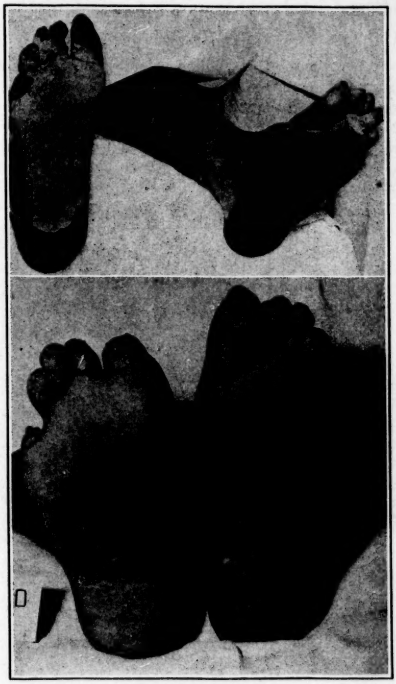

FIGURE 8. *The Results of Conservative Treatment of Gangrene in a Case of Trench Foot. (Reproduced by courtesy of Col. R. H. Patterson and Maj. F. M. Anderson, M.C., A.U.S., Letterman General Hospital.)*

symptoms by hastening the absorption of collagen and fibrous tissue and by increasing the superficial and collateral circulation through the injured extremities. This operation should therefore be seriously considered in selected cases and warrants extensive trial and critical observation. Although Harris and Maltby[3] have been impressed by the frequent association with vasospasm, this has in our experience been the exception rather than the rule. Only 3 of 36 soldiers with severe trench foot from Attu and 2 sailors had this complication to a well-marked extent. All were dramatically improved by sympathectomy (Fig. 9). In addition, a limited number of cases with atrophic, rigid feet, as well as certain cases of delayed wound healing

that did not exhibit vasospasm, have been treated by lumbar sympathetic ganglionectomy. The results to date have been gratifying. It is therefore proposed that unilateral sympathectomy be tried in a representative series of cases of bilateral severe trench feet exhibiting atrophy, rigidity and fibrosis. For completeness the series should include cases both with and without vasospasm.* At the time of operation a biopsy, to include a bit of skin, subcutaneous tissue and extensor brevis digitorum muscle, should be obtained from the dorsolateral aspect of each foot.[12] This biopsy should be repeated three months postoperatively so that the effects of sympathectomy can be finally and accurately assessed by comparing the tissues from sympathectomized and nonsympathectomized feet.

FIGURE 9. *A Case of Immersion Foot Eleven Months after Exposure.*

This photograph shows fibrosis and an indolent ulcer of the big toe. These feet were cyanotic, cool and sweaty, but the arterial pulsations were maintained. There was a good response to paravertebral procaine block and to lumbar sympathectomy, which was followed by vasodilatation, healing of the ulcer and relief from the aching pain.

Before closing, a word of caution must be interjected. In seeing a large number of late initially *mild* cases of trench feet, one of us (W.B.S.) has become impressed with the susceptibility of such cases to an hysterical prolongation of symptoms and disability, and with the need for correction of purely mechanical dysfunctions secondary to prolonged disuse, muscle weakness and contractures. Arch supports and both orthopedic and psychiatric evaluation are imperative. In the *severe* cases every effort should be made to avoid early radical amputation. As in frostbite, delayed amputations result in the loss of only a few toes or the distal portion of a foot, and almost never the loss of an entire foot. This was demonstrated conclusively by Captain Lesser at the McCaw General Hospital in the cases of trench foot evacuated from Attu (Fig. 4).

*Cases with vasospasm are intended to include all patients with cold, cyanotic feet with or without excessive sweating that respond effectively to diagnostic procaine block (White[18]).

In conclusion, the lesions of trench and immersion foot can frequently be prevented by prophylactic measures of foot hygiene in troops campaigning under winter conditions and by safety measures at sea. Early emergency treatment largely determines how much of the foot and toes can be saved and how long the disability will continue. Late forms of therapy should include orthopedic and psychiatric measures, as well as sympathectomy in selected cases. Future efforts to improve the handling of these conditions should include further studies on the effects of climate and protection from exposure, widespread instruction in foot care and first aid and critical evaluation of the effect of sympathectomy on the absorption of fibrous tissue and collagen, as well as on the relief of pain.

SUMMARY

Trench foot and immersion foot are similar clinical entities that differ from frostbite in the type of exposure and the reaction of the tissues and their method of recovery.

Three stages in the course of these syndromes are described: the initial response to cold short of actual freezing of the tissue cells, the early period of recovery, characterized by painful hyperemia, and the residual effects of fibrosis.

Initial treatment is similar to that for burns, but should include cooling to reduce the oxygen demands of the skin to a level compatible with the flow of blood through damaged subcutaneous vessels.

Late treatment consists of conservative minimal amputations, exercises and physiotherapy to decrease tissue fibrosis and joint stiffness and sympathectomy in selected cases with residual circulatory insufficiency.

Gangrene of the toes and distal portions of the feet constitutes a serious problem in trench foot, but is rare in immersion foot, in which the lower extremities are less liable to trauma and infection.

Prolonged partial disability is frequent in both conditions.

Orthopedic and psychiatric factors must be taken into consideration.

Improvement in protective clothing, widespread instruction in foot care and first aid and a critical evaluation of the response of the fibrosed tissues to sympathectomy are in order.

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Discussion

Dr. Eugene E. O'Neil, Boston: These cases of trench foot and immersion foot, I dare say are not very much unlike those of trench foot that occurred in the last war, several of which I saw. I have seen a few of the present cases at the United States Marine Hospital, and all of them appeared to have taken on the rather late phase that Dr. White has emphasized; that is, they showed marked vasomotor disturbances — so marked, as a matter of fact, that they had all the earmarks of well-advanced Buerger's disease. When subjected to lumbar sympathectomy, as was done if the operation was indicated and if their collateral potential appeared sufficient to be developed in this manner, these patients improved almost without exception.

It occurred to me that, in view of what Dr. White has said about the hyperemic stage of immersion foot, it might be well to inquire from some of these sympathectomized patients what had happened shortly after the trench foot developed. Two of them stated that for two or three weeks following the onset they went through what was apparently a hyperemic stage. The feet were swollen and blistered and were extremely hot. Seeing these cases in the acute stage, one would think that they had been sympathectomized, but as time went on they have taken on the peculiar picture of progressive vasomotor disturbance and have been improved by sympathectomy.

Captain William B. Scoville: Within the Army, trench foot constitutes a most serious disability, far more serious than it is in civilian life. Rarely do any but the mildest cases return to combat duty, and hospitalization generally exceeds six months. This is because the disability prevents marching and standing, especially in inclement weather. I am told that the Russians consider these casualties of so serious a nature that they have gone to extraordinary and unique prophylactic lengths to prevent their recurrence. In their usual definitive fashion, they assign each soldier going to a cold climate to a companion, each man acting as the guardian of the other's feet. If one soldier gets a blister or frostbite, both soldiers are held responsible and both are liable to be shot — so the story goes. By this method, solicitude over one another's feet was simply intense.

In the northwest United States I saw severe cases of trench foot resulting from the Attu campaign. Thirty-five cases were followed by Captain Albert Lesser. All were gangrenous or near gangrenous, and 60 per cent required late conservative amputations of toes or portions of the feet. Even in such severe cases, only 3 showed evidence of vasospasm. From this small series, I concluded that constitutional autonomic instability with vasospasm is not a predisposing cause of trench foot. This has been borne out by Captain White's studies. On the other hand, I was impressed by the extreme prevalence of vasospastic disease in soldiers stationed in the cold climates of the Alaskan and Northwest theaters. A great number of these cases occurred in soldiers who had spent their entire life in warm climates. Although vasospasm is rare in trench and immersion foot, sympathectomy may have some place in hastening the reabsorption of scar tissue and collagen — common sequelae in trench foot, as shown by Captain White and Dr. Warren. Only further research can settle this point. Small subcutaneous biopsies taken from both feet before and after a unilateral sympathectomy should give the clue.

My studies on sympathectomized cases of trench foot first whetted my interest in the effects of sympathectomy on the treatment of chronic indolent wounds and infections of the feet. The results of such a procedure in these cases have been most gratifying, so much so that we now recommend it in the majority of cases that have failed to heal within six months' time regardless of the presence of vasospasm. I have in mind several such cases, and mention a case of osteomyelitis of the great toe following a gunshot wound that had drained continuously for eight months, with removal of sequestrum two months previously. Pain and drainage had continued. Nine days after sympathectomy drainage stopped and the pain was immediately and progressively ameliorated. In another case, an indolent low-grade infection in the nail beds of both great toes followed recurrent attempts at removal of the matrix of ingrowing toenails by an overzealous young medical officer who had used every known method to kill the matrix of the nail, including scalding the nail bed with hot fluids. When seen by us, this patient had not put either foot to the ground for over a year because of pain and still had unhealed granulations in the nail beds. Unilateral sympathectomy with the other foot used as a control gave most gratifying results in healing and epithelialization, as well as in subsidence of the pain.

I offer two final words of caution concerning the therapy of trench foot. The first is a plea for extreme conservatism in amputation. In Lesser's series of severe cases, the majority of surgeons who saw such cases on their admission to Army hospitals cheerily advised, "You may as well amputate now as later," but after four to six weeks of conservative and meticulous care the healing of apparently hopelessly ulcerated toes and feet was startling. The second word of caution lies in the psychiatric field. Trench foot is closely akin to low-back pain in its predisposition toward neurosis. The drama of onset, the vagueness of the pain and the absence of objective disease in the mild cases all make it easy for these patients to capitalize on their disability. When patients continue to complain of pain for periods of longer than six months without objective evidence of peripheral vascular disease or tissue damage, a neurosis should be suspected.

Dr. James C. White, Boston: The term "Raynaud's disease" has been loosely used here. It should be qualified so as to indicate cold, clammy, cyanotic feet that show a dramatic improvement in circulation following procaine block or lumbar sympathetic ganglionectomy. I do not believe that these men who have been exposed to cold and moisture have actual blanching of the toes, as I have not yet seen one with this condition. They do have continuous excessive vasoconstriction, with a tendency to excessive perspiration in the extremities.

Another question of interest is why this phenomenon is so frequent. Many people have a tendency to cold, moist hands and feet, and this is often greatly increased after emotional stress. Dr. Frank Fremont-Smith and Dr. Stanley Cobb discovered a few cases of typical Raynaud's disease in which the first bouts of phasic asphyxia developed on the breaking off of an engagement, the death of a husband, financial failure or some other cause of severe emotional disturbance. These men whom we have been discussing have, of course, been through an extremely severe emotional disturbance. If they go on having incapacitating pain and are bandied about in service hospitals and their compensation is not adjusted, they have every reason to develop chronic vasospasm in their feet.

MEDICAL PROGRESS

THE TREATMENT OF INFECTIONS WITH PENICILLIN (Concluded)*

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Staphylococcal Infections

Penicillin has proved to be the most effective chemotherapeutic agent yet discovered for the treatment of staphylococcal infections.[55, 56, 62] The usual mortality rate of 80 per cent in untreated cases of staphylococcic bacteremia[63] has been reduced with penicillin treatment to 20 per cent or even less. Doses between 150,000 and 300,000 units a day are usually desirable until the infection has been controlled. The daily dosage may then be reduced to 120,000 units. It has been widely recognized that in severe staphylococcal infections striking improvement may not be observed for several days after the beginning of treatment. It is not unusual, however, for the patient to begin to look and feel better several days before the temperature returns to normal. Not infrequently the blood culture may still be positive when the first signs of improvement are noticed. The rapidity of the response to treatment, as well as the end results, are influenced by several factors, including the severity of the primary lesion, the number of metastatic lesions, the accessibility of both primary and secondary foci to surgical drainage and the general condition of the patient. The poorest results are obtained when the infection localizes on the endocardium, giving rise to a bacterial endocarditis. Even this complication, however, occasionally responds to treatment with penicillin.

Although surgical drainage is frequently an important adjunct to penicillin in the treatment of staphylococcal bacteremia, there are certain infections in which, not infrequently, the withholding of operative measures may shorten the recovery period and result in less permanent dysfunction or disfigurement. Since carbuncles, for example, respond very well to penicillin treatment, surgical intervention, except for the evacuation of obvious collections of undrained pus, no longer seems to be necessary. Treatment for ten to fourteen days has usually effected complete resolution of the infection, although the separation of slough and the epithelialization of denuded areas often has not been complete for another one to three weeks.

Acute hematogenous osteomyelitis appears to be best treated without surgical drainage, except in the presence of a large soft-tissue abscess. Under penicillin treatment alone the rapidity of clinical recovery and the extent of healing and repair of the bone appear to surpass that of cases treated with surgical drainage.[64] An exception to this statement must be made for those cases in which a suppurative arthritis is also present. In such patients there is a great possibility that the joint will be destroyed unless penicillin can be introduced directly into the joint space. When a suppurative arthritis is present, it seems advisable to perform early whatever surgery is necessary to facilitate the local instillation of penicillin into the involved joint once or twice a day. It has been desirable in acute osteomyelitis to continue treatment for at least two or three weeks, and in severe cases with multiple lesions longer treatment has been necessary. Since the roentgenographic changes in the bone do not keep pace with the clinical progress in this disease,[14, 64] reliance has had to be placed on the clinical signs of recovery in determining when to stop treatment. Not infrequently the destruction of bone has been most extensive at a time when it was obvious clinically that the patient had recovered. Even though treatment was stopped at this point, rapid repair of bone with a striking return toward a normal bone architecture usually took place in the next few weeks or months. In occasional cases that were treated extremely early, no signs of bone destruction developed in the roentgenograms.

Kirby and Hepp[65] have reported excellent results with penicillin therapy in the treatment of osteomyelitis of the facial bones. When sequestrums were present, surgical treatment in addition to the use of penicillin was necessary to effect complete recovery.

Anderson, Howard and Rammelkamp,[43] in a study of the management of chronic hematogenous and traumatic osteomyelitis, found that when sequestrums were present it was necessary to remove them surgically to obtain satisfactory healing. These authors were able to secure an arrest of the disease with the disappearance of all local and constitutional signs of active infection in 70 per cent of their patients with chronic osteomyelitis. Prolonged therapy varying from two to six weeks was found to be necessary to achieve the best results. Occasionally the therapy had to be repeated when relapses occurred. The primary closure of wounds

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after sequestrectomy, together with the local administration of penicillin postoperatively, greatly shortened the recovery period.

Staphylococcal pneumonia has responded well to penicillin. In the absence of secondary foci recovery is usually complete in one to two weeks. The treatment of staphylococcal empyema with penicillin introduced into the empyema cavity has usually resulted in a decrease or disappearance of fever and a marked lessening of toxicity. In most cases, however, the exudate has not become sterile and thoracotomy has been necessary to effect full recovery.

Streptococcal Infections

Hemolytic streptococcus infections are even more susceptible to the action of penicillin than are staphylococcal infections. In general the response has been similar to that seen with the sulfonamides, although in some cases the therapeutic effect has been even more rapid. Doses of 100,000 to 150,000 units a day are usually effective. Depending on the severity of the infection, treatment is continued until the temperature has been normal for two to five days.

Anaerobic streptococcus infections have been irregular in their response to penicillin since there is considerable variation in strain sensitivity to the drug. The sulfonamides are never effective in such infections, and a trial course of therapy with penicillin is indicated when such infections arise. Prolonged treatment may be necessary, particularly if there is an intravascular focus of infection, such as a thrombophlebitis.

Infections due to nonhemolytic streptococci that have been treated with penicillin have consisted almost wholly of cases of subacute bacterial endocarditis. Early attempts to treat this disease with penicillin were unsatisfactory because only small and inadequate doses could be given.[55] More recent experience, involving the use of doses of 200,000 to 300,000 units a day for periods of two or three weeks, has produced at least temporary arrest of the infection in more than 50 per cent of the cases.[66–68] From the evidence now available an initial course of treatment of 200,000 to 300,000 units a day for three weeks should be satisfactory in most cases. If by the end of a week the blood culture has not become negative, the dose should be increased. Patients who have relapsed after two or three weeks of therapy have been treated with more prolonged courses of treatment, with apparently successful results in a few cases. Cases have been encountered, however, in which it has been impossible to control the infection even when treatment has been continued for two or more months. The available evidence indicates that penicillin is just as effective in this disease when given by intermittent intramuscular injection as it is when given by continuous intravenous infusion. The use of heparin in conjunction with penicillin has been recommended,[66] but this does not seem to be necessary and may constitute an added hazard to the patient.[69]

Strains of nonhemolytic streptococci vary in their sensitivity to penicillin, although the great majority are sensitive to the drug.[35] Enterococci, which cause about 10 per cent of cases of subacute bacterial endocarditis, are relatively insensitive to penicillin, and cases of endocarditis caused by these organisms have not responded to treatment. In view of the large amount of penicillin that must be given in bacterial endocarditis, it is advisable to investigate the sensitivity of the organism in each case before or at the beginning of treatment. In patients who relapse, the infecting organism usually has not shown a significant decrease in its sensitivity to penicillin.

It is of considerable interest that, for several weeks after the completion of treatment, patients whose blood cultures remain negative and who otherwise appear to be free of active disease have often exhibited petechiae and other embolic phenomena. In many of these patients the embolic phenomena have ceased after a short time and the patients have continued to remain well without further treatment. For this reason, it has been assumed that these episodes were caused by bland or sterile emboli. Occasionally embolism of a cerebral vessel has caused death. A few patients after recovering from the infection develop cardiac failure, which may progress and end fatally within a few months after treatment.

Gonococcal Infections

The original observation by Mahoney et al.[70] that penicillin produces rapid and permanent cures in gonococcal infections has been fully confirmed.[71] About 96 per cent of gonococcal infections that are confined to the lower genital tract in either the male or female are cured by the administration of a total of 100,000 units of penicillin. The remaining 4 per cent usually respond to more intensive or prolonged treatment. No proved cases of penicillin-resistant gonorrhea have yet been encountered. Although varying schedules of administration have been used, the intramuscular injection of 20,000 units every two or three hours for five doses appears to be the most convenient. Such a treatment schedule is readily adaptable to office or outpatient practice. Gonococcal infections complicated by arthritis, prostatitis, salpingitis, epididymitis or endocarditis require more prolonged treatment. Whether penicillin is more effective than the sulfonamides in the treatment of gonococcal arthritis remains somewhat in doubt.

Meningococcal Infections

Experience with the treatment of meningococcal meningitis has varied. Rosenberg and Arling[72] reported recovery in 65 of 66 patients treated with

penicillin. Their report, however, does not make clear how many of their patients received sulfonamides as well as penicillin. Meads et al.,[73] on the other hand, in a more critical study found that neither the bacteriologic nor the clinical signs of improvement were so rapid in patients treated with penicillin as in those treated with sulfonamides. Furthermore, 2 of their 9 patients treated with penicillin eventually required sulfonamide therapy to effect full recovery. At the moment, it appears that the sulfonamides are at least as efficient as penicillin in treating meningococcal meningitis and that they constitute a much more convenient and economical form of therapy. Penicillin may well be found useful in combination with the sulfonamides in the treatment of fulminating cases, and it is certain to have a place in the treatment of patients who do not respond to sulfonamide therapy or in whom sulfonamide treatment is contraindicated.

Pneumococcal Infections

Tillett[28] has shown that pneumococcal pneumonia and empyema respond readily to penicillin treatment. A dosage of 100,000 units a day for three or four days is adequate in most cases of pneumonia, although occasional patients require more prolonged and intensive treatment. Pneumococcal empyema has been treated successfully by injections of penicillin repeated daily or on alternate days for three to four injections. From the results now available, it seems that a high percentage of cases do not require surgical treatment. A thickened pleura with or without a sterile exudate may persist for several days or even weeks after treatment is completed. Organization of the exudate and permanent collapse of the lung may rarely develop, but the greatly shortened period of illness and disability that results from nonsurgical treatment is a strong endorsement for this form of therapy, provided the physician is alert for the possible appearance of the above-mentioned complications.

Pneumococcal meningitis has been successfully treated with a combination of intrathecal and intramuscular penicillin.[74] The fatality rate with such treatment in a large unselected series was approximately 55 per cent.[75] In a smaller group of cases, Waring and Smith[76] have reported the recovery of 11 of 12 patients following the combined use of penicillin and the sulfonamides. Although even combined therapy has failed in fulminating infections and cases that are treated late,[29] the use of both drugs appears to be rational and should give better results than when either drug is used alone. How long to continue therapy in this disease is a difficult question to answer, and undoubtedly the need for therapy varies from patient to patient. In cases that are treated with penicillin alone, it is usually necessary to continue intrathecal and systemic therapy for at least two weeks, but in occasional cases it is necessary to continue treatment for many more weeks before the infection is eradicated.[18] When patients are receiving both penicillin and a sulfonamide, it has been possible to discontinue penicillin seven to ten days after beginning treatment, but it appears wise to continue the sulfonamide for at least two weeks after apparent recovery. The usual guides by which one measures progress may be lacking. After one or two days of intrathecal penicillin administration, the smears and cultures of the spinal fluid almost invariably fail to demonstrate the presence of organisms. It is known, however, that if treatment is stopped after the first negative bacteriologic reports are received, relapse is likely to occur. In certain patients who recover from the infection, residual damage to the central nervous system of greater or lesser extent has been observed.

Acute pneumococcal endocarditis can be successfully treated with penicillin, but the percentage of recoveries is not so great as in subacute bacterial endocarditis caused by nonhemolytic streptococci.

Clostridial Infections

The in-vitro activity of penicillin against the clostridial group of organisms has been confirmed by clinical studies. Jeffrey and Thomson,[77] in a study of 33 cases of gas gangrene treated with penicillin, found a mortality rate of 36 per cent. These authors emphasize, as do all other workers who have had experience with the problem, that the adequate surgical removal of all necrotic and devitalized tissue is the most essential therapeutic procedure in the management of gas gangrene. Five of their patients were seen late in the disease when surgery was not possible, and all of them died, despite treatment with penicillin. These authors believe that a dosage of 15,000 units every three hours for three to four days will control the infection in cases in which all the infected tissue can be removed surgically. In cases in which this is not possible, it is desirable to continue treatment for five to ten days. The administration of antitoxin is also of great value. Jeffrey and Thomson believe that with early and adequate surgery, aided by the administration of penicillin and antitoxin, the mortality rate in gas gangrene in battle casualties can be reduced to 20 per cent. Cutler and Sandusky[78] treated 7 patients with gas gangrene, 6 of whom recovered. It is noteworthy that in 5 of their patients gas gangrene developed while the patients were receiving prophylactic penicillin therapy. Following extirpation of the diseased tissues all these patients recovered.

A few cases of tetanus have been successfully treated with penicillin and antitoxin.[79] The group is too small to evaluate the role that penicillin played in recovery.

Syphilis

In October, 1943, Mahoney et al.[80] reported on the favorable action of penicillin in the treatment of early syphilis. Following this report intensive studies of the treatment of early syphilis, neurosyphilis and congenital syphilis have been carried out by a group of co-operating clinics.[81–84] Final evaluation of their results will not be possible for several years. Preliminary reports indicate that a course of sixty injections of 20,000 units each given intramuscularly at three-hour intervals for seven and a half days probably represents the minimum dosage schedule that is effective in primary and secondary syphilis. It is not unlikely that more prolonged or more intensive treatment will prove to be necessary. Studies on neurosyphilis indicate that even larger doses are needed and that the results are much more irregular than those in early syphilis. Late cutaneous and osseous syphilis apparently respond promptly to penicillin treatment. No work has been reported yet on the action of penicillin in latent syphilis. A few cases of congenital syphilis have been treated in which good results have been obtained. It is agreed by all workers who are investigating the problem that the treatment of syphilis with penicillin is still in the stage of preliminary investigation and that no schedule of treatment can yet be recommended for routine therapy.

In the treatment of syphilis with penicillin, the incidence of Herxheimer reactions has been high. The reactions that have been observed have consisted of fever, malaise, headache, rash and painful swelling of the primary lesion and the regional lymph nodes. These reactions usually occur during the first day of treatment and disappear after twenty-four or forty-eight hours. They are not considered to be an indication for stopping treatment.

Miscellaneous Infections

Most strains of Actinomyces are sensitive to penicillin, and a few cases of actinomycosis have been successfully treated.[29] Repeated courses are frequently necessary to keep the infection under control.

Anthrax responds well to penicillin, and it seems reasonable to predict that the drug will become the treatment of choice in this disease. Murphy et al.[85] have reported the successful use of penicillin in 3 cases of uncomplicated cutaneous anthrax. They believe that a dosage of 100,000 units a day for three or four days should be adequate in the average case. At least one patient with bacteremia has been treated, with a prompt and full recovery resulting.

The two causative agents of rat-bite fever, *Spirillum minus* and *Streptobacillus moniliformis*, are both sensitive to penicillin in the laboratory.[86] Clinical cases caused by the latter organisms have been reported to respond favorably to treatment with penicillin.[87]

A preliminary report on the successful treatment of yaws with penicillin has recently been published.[88] One case of Weil's disease has been reported in which penicillin was administered and recovery ensued.[89] The author admits that the evidence that the drug had an effective therapeutic action in this case is not conclusive.

Penicillin is active in vitro against *Corynebacterium diphtheriae*. A few cases of clinical diphtheria have been treated with a combination of antitoxin and penicillin with results that are difficult to evaluate.[90] There is no reason to expect that penicillin will supplant antitoxin as the chief therapeutic agent in diphtheria. The supplementing of antitoxin with penicillin in cases of laryngeal diphtheria and diphtheria gravis may, however, prove to be valuable, although the evidence to support this procedure remains to be accumulated. Preliminary efforts to treat diphtheria carriers with penicillin have not met with success.[91]

Penicillin is already being adapted to the problems that are peculiar to various medical specialties. Dunnington and Von Sallmann[92] and Keyes[93] have reviewed the use of penicillin in ophthalmology. Infections of the conjunctiva and cornea usually respond well to local treatment when the infecting organism is susceptible to the action of penicillin. The drug may be administered in drops or in an ointment. Infections of the internal structure of the eye are more difficult to treat because of the poor penetration of penicillin. Special methods for administration, such as iontophoresis, the use of a corneal bath and direct injection of the drug into the anterior chamber of the eye, are usually necessary.

Swanson and Baker[94] have used penicillin in the management of acute otitis media, acute mastoiditis, acute labyrinthitis and chronic otitis media. When the infecting organisms are sensitive to penicillin, excellent results have usually been obtained. In selected cases penicillin therapy alone may be successful; in other cases surgical procedures must also be employed.

Johnson et al.[95] have shown that the local use of penicillin postoperatively in patients with acute mastoiditis permits the safe primary closure of incisions and greatly shortens the recovery period. Putney[96] has reviewed the successful use of penicillin in the treatment of some of the more serious complications of infections of the nose and throat. Sale and Diamond[97] have described the treatment of chronic suppurative maxillary sinusitis by local instillations of penicillin.

In the field of plastic surgery, Hirshfeld et al.[98] have reported that the systemic administration of penicillin greatly increases the percentage of successful skin grafts applied to infected surfaces.

The use of penicillin in infections of the skin

has been discussed by Roxburgh et al.[99] and by Taylor and Hughes.[100] Gingivitis and stomatitis caused by the Vincent's organisms have been effectively treated by the use of penicillin pastilles.[101]

Prophylactic Administration of Penicillin

The prophylactic use of penicillin is just beginning to be studied. White et al.[102] have shown that penicillin administered intramuscularly for one week preoperatively and for two weeks postoperatively in doses of 150,000 units daily is of great value in preventing postoperative pyogenic infections following lobectomy or pneumonectomy. Their cases included patients on whom operation was performed for bronchiectasis, multiple lung abscesses, tuberculosis and carcinoma. In 21 patients treated prophylactically with penicillin, no cases of empyema developed, whereas in 20 control patients, 12, or 60 per cent, developed pleural suppuration. Cutler et al.,[103] on the other hand, in a study of the prophylactic use of penicillin in conjunction with early definitive surgery in wounds sustained in aerial warfare did not find that the use of penicillin lowered the incidence of infected wounds.

Diseases Uninfluenced by Penicillin

A review of the present status of penicillin therapy would not be complete unless it included mention of those diseases in which penicillin has not proved to be of therapeutic value. The list of such diseases, as compiled by Keefer,[104] is reproduced, with additions, in Table 3.

Since penicillin has no effect against infections caused by gram-negative bacilli, it is not to be expected that the drug will prove to be of value in the treatment of peritonitis following a ruptured viscus, except in those cases in which organisms sensitive to penicillin happen to play a significant role. Fauley et al.[107] have reported that penicillin given early will completely control experimental peritonitis in the dog. These workers, however, do not include any bacteriologic findings in their report.

Table 3. *Diseases in Which Penicillin Therapy is Ineffective.*

All gram-negative bacillary infections	Coccidiomycosis
Tuberculosis	Malaria
Toxoplasmosis	Poliomyelitis
Histoplasmosis	Blastomycosis
Acute rheumatic fever	Nonspecific iritis and uveitis
Lupus erythematosus (diffuse)	Moniliasis
Infectious mononucleosis	Virus infections
Pemphigus	Cancer
Hodgkin's disease	Rheumatoid arthritis[105]
Ulcerative colitis	Granuloma inguinale[106]
	Leukemia (acute and chronic)

Toxic Reactions

Despite the greatly increased clinical experience with penicillin during the past year, no reports have appeared to cause any revision of the early opinion regarding the drug's lack of significant toxicity for man. To date no harmful effects on the liver, kidneys or hematopoietic system have been observed following its administration. A few minor untoward reactions have been encountered.

From 2 to 5 per cent of patients treated with penicillin develop urticaria. The urticaria may appear on the first day of treatment, or it may not become apparent until several days after treatment has been completed. It usually develops during the second week of treatment. Occasionally it may be quite severe, but in most cases it is mild and frequently disappears even though treatment is continued. If penicillin is administered at a later date to a patient who developed urticaria with a previous course of treatment, urticaria may or may not reappear. Most workers do not believe that urticaria is a contraindication to the continuation of treatment or to the readministration of the drug at a later date. In the rare case in which urticaria is marked, the patient's severe discomfort may necessitate stopping treatment.

Much more unusual is the appearance of an erythematous vesicular rash.[108] I have seen a patient in whom a very severe rash of this type appeared twenty-four hours after the beginning of treatment in areas where there had been a severe ringworm infection four years previously.

Pain on intramuscular injection is encountered with varying frequency. It has been shown conclusively that impure preparations are the most irritating.[16] There is also no question that the technic of administering the drug has much to do with the amount of discomfort or lack of discomfort that occurs. When a portion of the drug is given subcutaneously by error, the degree of discomfort appears to be increased.

I have seen 4 cases in which foot drop developed in patients who were receiving intramuscular injections of penicillin into the buttocks. For this reason, great care should be taken to avoid injecting penicillin into the sciatic nerve or its immediate neighborhood. If the upper outer quadrants of the buttocks are used for the injections, the nerve should be easily avoided.

After multiple intravenous injections, thrombosis of the veins at the sites of the injection may occur. This event appears to be related more to the technic of performing the venipunctures than to irritation from the injected solution. In patients receiving the drug by a continuous intravenous infusion, however, the development of a painful thrombophlebitis in the vein being used is not infrequent. This reaction is often accompanied by chills and high fever. Changing the needle to another vein usually does not relieve the symptoms, and in most cases it becomes necessary to change from the intravenous to the intramuscular route of administration.

The penicillin preparations that are now being distributed are tested for pyrogens before being

released by the manufacturers. The febrile reactions due to impurities in the drug that were occasionally encountered in the early days of penicillin treatment are no longer seen. Drug fever analogous to that seen in sulfonamide therapy has not been reported. Occasionally patients have been observed who maintain a low-grade fever after the clinical signs of infection have disappeared. In several of these cases, the temperature has returned to normal when penicillin was discontinued.

In rare cases the administration of penicillin has been accompanied by diarrhea, with or without abdominal cramps. Nausea and vomiting caused by penicillin have not been described. On the contrary, a return of appetite is one of the earliest signs of a favorable response to penicillin therapy. With the use of some of the early preparations various minor reactions were seen from time to time, including headache, flushing of the face and pain in the testes. With the preparations now in use, these reactions are not being reported.

The maximum dose of penicillin that can be given safely to man has not yet been determined. Doses as large as 4,000,000 units a day have been given in several cases without ill effect. At present there are no known contraindications to the administration of penicillin, although there may be reason for hesitation in administering large initial doses to patients with cardiovascular or congenital syphilis. So far as is known, penicillin is not incompatible with any other drugs or articles of diet.

* * *

Penicillin has been shown to be a potent, nontoxic, antibacterial agent against many important pathogenic bacteria. In the treatment of almost all infections caused by these organisms, penicillin is the most effective chemotherapeutic agent that has yet been discovered. Its use in many of these infections, either alone or in combination with other established forms of therapy, has resulted in a lowering of the mortality rates, a shortening of the periods of illness and a reduction in the number of complications. In many diseases, sufficient experience has accumulated to permit the formulation of fairly definite concepts regarding the effectiveness of penicillin and the best methods for its employment. In other infections, experience has been limited to a few experimental efforts that merely hint at the possibilities of penicillin therapy.

In the treatment of infections with penicillin, early treatment, adequate dosage and the continuation of treatment until the infection is eradicated are essential for obtaining the maximum results. Likewise, in planning therapy, proper consideration must be given to the known facts concerning the absorption, excretion and distribution of penicillin in man. In many cases the concomitant use of other therapeutic procedures of established value, including general supportive measures, surgery and the administration of specific antiserums, are necessary to effect recovery.

The drug cannot be expected to have a favorable effect on the course of diseases other than those infections in which the causative organisms are known to be susceptible to the action of penicillin.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31151

PRESENTATION OF CASE

A twenty-four-year-old farmer entered the hospital because of severe sacral pain.

Two months before entry, without known preceding trauma, he began to have intermittent dull, aching pain in the right half of the sacrum. Two weeks later he received three blows over this area that caused severe pain. Following this the pain persisted, was sharp and was aggravated by motion, coughing and sneezing. X-ray studies of the lumbosacral spine six weeks before entry were allegedly negative.

One month before admission he spent ten days in a community hospital, where he was found to have fever and slight leukocytosis; he had no bowel movements for eight days. During the month before entry his back had been stiff and cutting pains began to occur, extending across the shoulders and in the arms. These lasted from a few minutes to several hours. One week before admission he felt "pins and needles" in his right hand, arm and shoulder, and a sharp pain just below the right costal margin. The pain frequently shot from the lower back down the posterior aspect of the right leg to the heel. He had spent most of the month preceding entry in bed and finally could scarcely move because of pain. During the earlier part of his illness he lost 25 pounds. He had become extremely weak. For about a month he had noted some difficulty in starting the urinary stream.

Physical examination revealed an emaciated, anemic-looking man who complained of excruciating pain in the lower back on the slightest motion. There was generalized muscle wasting, most pronounced in the thighs. There were splinting of the chest and marked spasm of the abdominal muscles, with slight, diffuse abdominal tenderness and marked tenderness of the lower thoracic and lumbar spine and over the right sacroiliac joint. The knee and ankle jerks were diminished on the right side. The arm jerks, abdominal reflexes and plantar reflexes were normal. Sensation was normal. There was slight generalized lymphadenopathy. The heart and lungs were not remarkable.

The temperature was 99°F., and the pulse and respirations were normal. The blood pressure was 128 systolic, 68 diastolic.

Examination of the blood showed a red-cell count of 4,250,000, with 12.2 gm. of hemoglobin, and a white-cell count of 12,000, with 88 per cent neutrophils. The differential count and cell morphology were normal. The urine was normal, containing no Bence-Jones protein. The stools were guaiac negative. The serum calcium was 8.5 mg. per 100 cc., the phosphorus 4 mg., and the phosphatase 4.7 Gutman[1] units per 100 cc. The serum protein was 6.3 gm. per 100 cc. The sedimentation rate was 53 mm. in one hour. Hinton and Wassermann reactions were negative. A lumbar puncture revealed an initial pressure equivalent to 250 mm. of water and normal dynamics; the fluid was clear and colorless and contained no cells, the total protein being 21 mg. per 100 cc.

X-ray examinations revealed slight irregularity of the margins of the dorsal vertebras and of the sacroiliac joints, which were thought to be consistent with rheumatoid arthritis. There was some increased density of the cortices of the internal condyles of the tibias. A chest film, gastrointestinal series and barium enema were negative. X-ray films of the knees and shoulders were normal.

The pain in the lower back and sacral region continued to be severe. There was occasional urinary and fecal incontinence. The temperature was slightly elevated most of the time, but it was rarely over 100°F., although it did reach 102° on one occasion. The pulse averaged 90, and the respirations remained fairly constant at 20. One week after admission he was awakened by a severe steady pain in the right flank, radiating to the groin and testicle but not to the penis. This lasted twenty minutes. He admitted that he had previously had similar

*On leave of absence.

attacks, always on the right side. The right knee jerk became progressively less active. Two weeks after admission a firm, tender swelling measuring 6 cm. in diameter and elevated 1 to 2 cm. was noted on the upper part of the sacrum to the right of the midline. Additional films of the sacrum and lumbosacral junction showed an area of apparent destruction in the posterior superior spine of the ilium, where it articulated with the sacrum.

On the eleventh hospital day an operation was performed.

Differential Diagnosis

Dr. William A. Rogers: May we see the x-ray films?

Dr. Milford D. Schulz: The irregularity described in the dorsal spine looks more like old epiphysitis than anything else. The films show the lumbar spine and the dorsal spine to be otherwise normal, but on the film of the pelvis there is shown an area of rarefaction in the right wing of the sacrum that is indefinite in outline. It does not have sharp borders, and whether it is primary in the sacrum or the result of destruction by something metastatic to it cannot be determined on the information we have.

Dr. Rogers: I agree that the roentgenogram of the thoracic vertebras in the lateral view reveals an old epiphysitis and is not suggestive of other diseases that might involve the thoracic region, such as, tuberculosis and the rheumatoid group of vertebral-column conditions. The changes are not consistent with trauma, nor is there evidence of pyogenic infection. In the anteroposterior view of the lumbosacral region there is a suspicious area of increased radiability in the right ilium, near the sacroiliac joint, without definite demarcation. There are no appreciable margins about this area. The films are far from conclusive, however, by reason of the circumstance that the gas patterns overlying the right side of the sacrum are such as to make it quite difficult to be certain of definite bone change. The lateral view of the lumbosacral junction does not look abnormal.

The salient features in this case seem to be the patient's age, twenty-four years, and his incapacity of months rather than of days. There was a temperature elevation that averaged 100°F. but had not been over 102, and concomitant with this, the white-cell count had not exceeded 12,000 or, what is more important, it did not go over 15,000. I am struck with the circumstance that he had not only excruciating local pain but also corresponding referred pain, that is, to the posterior aspect of the thigh and leg. Consistent with the referred pain was the sharp diminution in the ankle jerk. The diminished knee jerk is not attributable to a lesion of the first sacral segment, as is the diminished ankle jerk, since it corresponds to the third lumbar segment. It may have been due to the wasting that was apparent in the quadriceps muscle. We also know that this patient had a good deal of urinary and rectal incontinence. There again, these functional changes are consistent with a serious deep lesion in the sacrum. We also know from the history that this man developed severe pain in the right flank that was accompanied by pain in the ilioinguinal and iliohypogastric distribution, the right groin and the testicle. This distribution of referred pain is consistent with a lesion of the right flank that may be in the right upper lumbar gutter, or it may come from the vertebral column — the twelfth thoracic or first lumbar segment. But the appearance of the twelfth thoracic and first lumbar vertebras in the roentgenograms does not suggest the presence of a lesion. The films are not too good, but it should be remembered that the man was in excruciating pain, associated with extensive splinting of the thorax and the abdomen, which might make it difficult to place him in the correct position for good films.

Another salient feature in this case is the splinting in the chest and abdomen. It is an outstanding clinical sign. The splinting is a reflex mechanism protecting either the contained viscera or the vertebral column or meninges in the thoracic or lumbar region. When extreme, it is suggestive of meningeal irritation. Lastly, he had no definitely localizing symptoms other than the subjective one of pain in the right side of the sacrum until several days before operation, at which time he developed a firm sizable mass in the upper half of the sacrum on the right side.

Are we dealing with infection, with congenital malformation, with injury, with new growth or with some metabolic disturbance, such as rheumatoid arthritis?

From the standpoint of acute infection, a pyogenic infection could have been the primary cause of this man's trouble. All pyogenic infections are not fulminating, and all do not produce a high elevation of the temperature or white-cell count. Against acute pyogenic infection, however, is the duration, two months, without evidence of abscess formation. Certainly roentgenograms taken one month following acute pyogenic infection of the sacrum should show changes. Usually a history of two or three days is consistent with osteomyelitis. The possibility of osteomyelitis of the sacrum is, however, real, but I do not believe that it is likely. In the chronic infections we have to consider syphilitic osteitis. We know that the Hinton and Wassermann reactions were negative. Tuberculosis should certainly have responded favorably to rest in bed for a month; instead the patient grew steadily worse, his symptoms intensified, and finally the mass appeared. Although this could have been a cold abscess, I believe that the likelihood of tuberculosis is not great.

Among the congenital malformations, low leptomeningeal and cauda-equina lesions can be ruled out by the absence of symptoms prior to two months ago and by the lumbar-puncture findings.

I am far more impressed by the probability of neoplasm in this case. Among the primary tumors, Ewing's tumor would be consistent with the temperature elevation and the leukocytosis. On the other hand, the patient was twenty-four years old, and Ewing's tumor usually, but not always, occurs in the first two decades. Furthermore, Ewing's tumor is usually confined to the shafts of the long bones, although it may occur in the pelvis and may be purely osteolytic. I am inclined to think that this is not a Ewing's tumor, although it is a possibility.

Multiple myeloma must also be considered. The lesion of multiple myeloma is rather apt to be circumscribed, and although it may be solitary for many months or even several years, it would scarcely give the roentgenographic appearance that this case shows.

Neuroblastoma produces osteolytic bone lesions. It is a possibility in this case but does not explain the fever or leukocytosis.

Of course, osteolytic bone sarcoma must be considered. The patient was on the borderline between the young and the old group, so that he could have had an osteolytic sarcoma from any of the elements of the bone. A tumor of the lymphosarcoma group, which includes lymphocytoma, lymphoblastoma and reticulum-cell sarcoma, would not be inconsistent with the findings in this case. There is not uncommonly fever with lymphosarcoma, and such a tumor might cause severe local pain in the right flank.

Because of the pain in the groin and testicle, renal-cell carcinoma should be discussed. This produces an osteolytic lesion in the bone and frequently metastasizes to the pelvic bones. There might have been a rupture of some of the rapidly growing cells in the renal region through the cortex of the cancer, with the initiation of the intense local and referred pain. This tumor, however, is not usually associated with fever. Many other carcinomas may metastasize to the pelvic bones.

In summary, I am inclined to favor neoplasm — either a lymphosarcoma as a primary lesion or a metastasizing osteolytic tumor, such as a renal-cell carcinoma, as a secondary lesion. It is possible that this man had a pyogenic infection or tuberculosis of the sacrum; he might even have had rheumatoid arthritis, but I believe that Dr. Ropes would agree that it is a rather atypical picture of rheumatoid arthritis.

Dr. Ronald C. Sniffen: Dr. Kubik, will you outline the terminal course regarding the neurologic findings?

Dr. Charles S. Kubik: As stated in the abstract, the patient had had pain between the shoulder blades and some numbness in the fingers. Several days after the biopsy, in the course of about two hours, he developed complete motor and sensory paralysis below the fifth thoracic level; following that he never again had pain below that level but continued to have extremely severe pain in the upper thoracic and lower cervical spine, in the upper part of the chest and in the arms. There were times when he had to be given 65 mg. of morphine subcutaneously every hour. He developed marked weakness and atrophy of the arms and hands and tumor masses in the occipital region. He died about two and a half months after entry or about two months after the biopsy.

Dr. Wyman Richardson: I looked at a blood smear before I saw this patient and was therefore unprejudiced. The smear showed a picture consistent with acute blood loss or tumor involving the bone marrow. Unfortunately I did not describe the smear in the record, but it showed a slight leukocytosis, with an increase in immature red cells and no toxic changes in the neutrophils, which suggested that no infection was present. There was something causing an increased output of cells from the bone marrow. Hemorrhage could have done that, but there was no history of hemorrhage. Therefore, by exclusion, some form of marrow tumor seemed likely. This diagnosis seemed to fit best with the clinical picture. I thought that the likeliest tumor was some type of lymphoma.

Clinical Diagnosis

Malignant tumor of ilium.

Dr. Rogers's Diagnosis

Malignant neoplasm, ? lymphosarcoma.

Anatomical Diagnosis

Ewing's tumor of sacrum, with widespread metastases.

Pathological Discussion

Dr. Sniffen: We made a diagnosis of "probable synovioma" on the biopsy material. After reviewing the section I was rather surprised that we gave it a name, for the section was poor and the tumor was undifferentiated.

The patient died eighty-three days after admission. He was extremely emaciated and had a severe anasarca, which included peripheral edema, ascites, hydrothorax and hydropericardium. The muscles of the right arm were atrophic. Over the sacrum on the right there were two decubitus ulcers. The right wing of the sacrum was destroyed by a tumor measuring 6.5 cm. in diameter. The right occipital bone contained a tumor of the same size, and the cerebral dura was studded with nodules that had penetrated that membrane but not the underlying arachnoid. At one point the superior longitudinal sinus had been invaded by the neoplasm. Otherwise the brain was unchanged, except for signs of in-

creased intracranial pressure. The spinal column from the fourth to eighth thoracic vertebra contained tumor, which had penetrated the epidural space and dura but not the arachnoid. The same situation prevailed for a distance of 13 cm. below the twelfth thoracic vertebra. Microscopic sections of the spinal cord showed early ascending and descending degeneration from about the midthoracic level. The ribs contained multiple tumor nodules. The lungs, liver, kidneys, pancreas and retroperitoneal and mesenteric lymph nodes were studded with metastatic nodules averaging a centimeter in diameter, with a maximum size of 4 cm. The adrenal glands weighed 26 gm. together, and each contained several small masses of tumor.

Microscopically the tumor was composed of undifferentiated cells with large, vesicular nuclei and an occasional nucleolus. The cytoplasm was scant and poorly defined. The cells were divided into groups by strands of delicate fibrous tissue. Our diagnosis was Ewing's tumor.

It is interesting to speculate on the origin of this type of tumor. Does it arise from the vascular endothelium, as Ewing[2] believed? Does it belong in the reticulum-cell-sarcoma group? Is it a bone tumor? One of the more recent ideas is that many of the neoplasms labeled Ewing's tumor are, in reality, metastatic neuroblastoma, a tumor originating from the primitive cells of the sympathetic nervous system. This theory was proposed by Colville and Willis[3] in 1933 and again by Willis[4] in 1940, who point out that there is no satisfactory clinical or roentgenographic distinction between Ewing's tumor and neuroblastoma and that radiosensitivity is not of real value in differentiating the two. Their first case was quite similar to the one under discussion except that the main and presenting tumor was in the thigh; the adrenal glands contained tumor nodules. The second patient had two large tumors, one in the thigh and the other in the line of the lumbar sympathetic chain, which ran through it. They cite the well-known papers of Hutchison[5] and Pepper,[6] who wrote of patients having small adrenal neuroblastomas with massive metastases to the skull or liver, which might have been mistaken for the sites of the primary tumor. It is unusual for a primary bone tumor to metastasize to lymph nodes as Ewing's tumor does so frequently. The complete confusion in the literature regarding the origin of Ewing's tumor cannot be denied.

Regarding the histology of these tumors, in neuroblastoma one often finds an arrangement of cells and fibrils that has the same configuration as the cells from which the sympathetic nervous system and the adrenal medulla develop. One mode of arrangement is in the form of a rosette — a ball-like aggregate of cells enclosing a meshwork of fibrils. These were beautifully demonstrated by Wright[7] in 1910, and Colville and Willis found rosettes in their cases. In neuroblastoma one may find more highly differentiated tissue in the form of ganglion cells, but Colville and Willis were unable to demonstrate such areas in their cases.

If there is truth in this theory, several practical points come to mind. Should amputation be undertaken if one is dealing with a metastatic tumor? Should routine roentgen therapy be given to the retroperitoneal tissue when a diagnosis of Ewing's tumor has been made after biopsy of a bone? Certainly the retropleural and retroperitoneal tissues should be investigated thoroughly in view of the fact that they may be harboring the primary tumor.

To come back to this case, and to reach no conclusion, I could find no resemblance between this tumor and a neuroblastoma. Therefore the diagnosis must rest at Ewing's tumor.

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CASE 31152

Presentation of Case

A thirty-six-year-old graduate nurse was admitted to the hospital because of irregular and profuse menstrual bleeding.

From the time of the menarche, at the age of sixteen, the menstrual periods were irregular and profuse, with considerable loss of blood on each occasion. At times there were long free intervals. At the age of twenty an appendectomy was performed, and a tube, said to be tuberculous, was removed. Following this she had long stretches of amenorrhea, followed by profuse bleeding, occasionally with clots, requiring eight to ten napkins a day for seven days. She received a variety of endocrine preparations, with no apparent effect until about four years prior to admission, when, following the administration of Antophysin, her periods became regular and normal for about two and a half years but then again became infrequent and profuse. For six months preceding entry she had had almost continuous flow.

The patient had always been obese, averaging 230 pounds. Two years before entry, while on a diet, she lost 75 pounds, but she had subsequently regained 50.

The patient's father died of tuberculosis when she was three years old, and a younger sister had pulmonary tuberculosis.

Physical examination revealed an obese woman in no acute discomfort. The skin was warm. There was no palpable adenopathy. The fundi were normal. The thyroid gland was not enlarged. The breasts were pendulous. The heart and lungs were negative. Slight tenderness was present on deep palpation in the left lower quadrant of the abdomen. A pelvic examination revealed a slightly enlarged uterus but was otherwise not remarkable.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 74 diastolic.

Examination of the blood revealed a red-cell count of 3,570,000, with 10 gm. of hemoglobin, and a white-cell count of 5100, with 66 per cent neutrophils, 27 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. There were no significant red-cell abnormalities on smear. The urine had a specific gravity of 1.020 to 1.030, with a 0 to + test for albumin; a few white cells were found in the sediment. The serum nonprotein nitrogen was normal, and the protein 5.9 gm. per 100 cc. A glucose tolerance test revealed a fasting level of 105 mg. per 100 cc., which rose to 185 mg. at the end of two hours and to 162 mg. at the end of three hours. The basal metabolic rate was +1 per cent. A blood Hinton test was negative. A tuberculin test (dilution unknown) was strongly positive.

Roentgenographic examinations of the skull, spine and urinary tract were negative.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Fred A. Simmons: Since this is a teaching clinic, I am going to mention a few points that might be instructive regardless of what the diagnosis may be. In any patient who is bleeding, no matter what age, we should include the tests that are available today for the ruling out of malignant disease. The most frequently practiced and probably the most accurate test at the moment is a diagnostic dilatation and curettage including cervical biopsy. We also have a fairly accurate test, the vaginal smear, which should have been carried out on this patient.[1] The laboratory has now studied vaginal smears from over 1200 cases, with an error of only 4 per cent in 95 cases of proved cancer. The point I am making is that anyone with this history should have cancer ruled out. I assume that this was probably the operation that they intended to do. I should also like to point out that in handling patients with profuse flowing at thirty-six years of age, a dilatation and curettage might better be carried out before giving any endocrine preparation. The assumption that Antophysin regulated the menstrual cycle implies that it was on an endocrine basis, but malignancy still cannot be ruled out. Antophysin is a proprietary name for chorionic gonadotropin.

That the patient had tuberculosis is quite likely in view of the family history and because of the reported tuberculous tube removed at the age of twenty. I believe that the general opinion of gynecologists in most parts of the country is that the proper treatment for such a condition, if it really were a tuberculous tube, is radical surgery, which would include removal of the uterus and both tubes and ovaries, since the process is apparently a hematogenous infection. This patient, according to the record, had no other signs of tuberculosis, and I rather doubt that she had it. I question then the pathological report of the operation at twenty years of age. Another thing that bothered me was that from the physical findings presented here I was unable to determine whether the patient had been married and whether she had ever borne children. It is fair to point out that the pelvic examination should include some comment whether the patient had a virginal or multiparous introitus.

Dr. Benjamin Castleman: The record merely states that the patient was unmarried.

Dr. Simmons: This fact does not help me unless it is fair to assume that she was a virgin, in which case I shall not go into the possibility of inflammatory disease other than tuberculosis. Of course, irregular bleeding of this nature can be due to gonorrhea and its sequelae. A pelvic examination should also include inspection of the cervix. All that may have been left out for the sake of brevity.

In summary, I am inclined to consider the tuberculous history and findings in the tubes to be irrelevant, although I cannot rule out tuberculous endometritis as the cause of the trouble. I am inclined to think that she did not have carcinoma, because she had lived so long with a history of bleeding. If we can believe the menstrual-cycle history, the amenorrhea followed by profuse flow is the perfect picture of functional uterine bleeding, metropathia hemorrhagica, endometrial hyperplasia or whatever you want to call it.

Metropathia hemorrhagica is a term applied to a specific type of functional uterine bleeding characterized by a state of continuous estrinism with hypoprogestinism, according to Albright.[2] It is frequently seen in women with general debility regardless of age, presenting itself as alternating amenorrhea followed by continuous flowing, usually without molimen and dysmenorrhea, which may have been present in the patient's normal menstrual cycle. Pathologically the endometrium is markedly thickened, with deep glands having the "Swiss cheese" appearance characteristic of the estrin effect.

Endometrial hyperplasia or what I prefer to call "endometrial dysplasia" is the pathological term applied to the clinical state described above. Func-

tional uterine bleeding or dysfunction of uterine bleeding refers to the abnormal state of flow, with or without amenorrhea, not precipitated by organic pathological disease and is a convenient pigeonhole for cataloguing vague irregular states of uterine bleeding.

I think that on the whole it is wise to suggest the need for diagnostic dilatation and curettage and biopsy. I shall make a diagnosis of endometrial hyperplasia on an endocrine basis; possibly there was a benign endometrial polyp.

DR. FRANCIS M. INGERSOLL: I agree entirely with the diagnosis of metropathia hemorrhagica associated with a hyperplastic endometrium; however, we often see patients with the same history in whom the endometrium is atrophic rather than hyperplastic. Apparently about 20 to 30 per cent of them originally had an overfunctioning endometrium.

CLINICAL DIAGNOSIS

Metropathia hemorrhagica.

DR. SIMMONS'S DIAGNOSIS

Endometrial hyperplasia (metropathia hemorrhagica?).

ANATOMICAL DIAGNOSIS

Tuberculous salpingitis and endometritis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The operation was a curettage, and a large amount of endometrium was removed. The diagnosis on microscopic examination proved to be tuberculosis. Following that operation a laparotomy was performed and the other tube and uterus were removed. We found tuberculosis in both the uterus and tube.

DR. INGERSOLL: Did they take out the cervix? I remember one case in this hospital in which someone first removed one tube, than at a subsequent operation took out the other tube and did a supravaginal hysterectomy and finally did a cervicectomy for tuberculosis.

DR. CASTLEMAN: The cervix was removed in this case.

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GOVERNMENTAL SUPPORT FOR MEDICAL RESEARCH

Senator Pepper, as chairman of a subcommittee of the Senate Committee on Wartime Health and Education, recently held a hearing at which a number of highly qualified persons were invited to discuss the question whether the federal government should continue in time of peace, as in war, to offer assistance through grants or in other ways to facilitate progress against disease through research. The Senator did not consider it possible or desirable for the Government to do all the work that its funds would finance. He was interested in determining how the universities, industries and the Government could best co-operate to achieve the highest development of medical research. Some of the information and opinions brought out at this hearing are of considerable interest.

Brigadier General J. S. Simmons, chief of the Preventive Medicine Service, Office of the Surgeon General, was the first person to be called. He said that one of the most important factors contributing to the excellent record of the Medical Department of the Army during this war has been the unique emphasis placed by the Surgeon General on the necessity for research in all fields of medicine. The comprehensive research program that has been developed and carried out by both military and civilian scientists has produced a wealth of new and fundamental knowledge and resulted in improved methods for the care of the wounded and the prevention and treatment of many of the diseases that afflict troops. The program included investigations in three general categories: projects developed within Army laboratories and field installations: projects developed in civilian institutions under Army contracts negotiated through the Office of the Surgeon General and projects developed for the Army in civilian institutions under contract with the Office of Scientific Research and Development. On the whole, the civilian response and the results obtained during the war afford an inspiring example of what can be accomplished through a well-organized, co-operative research program.

He said that the new knowledge made available had been immediately applied in the field. Three groups of studies were mentioned, any one of which more than justified the total cost of the program — those concerning the development of blood substitutes, of penicillin and of insect repellents and insecticides. In addition, new methods of immunization and other means of prophylaxis have considerably reduced the incidence and mortality of most of the important infectious diseases. The new weapons developed for the fight against these diseases, moreover, have also revolutionized the foreign quarantine program of the Army, Navy and Public Health Service, and they afford better methods for the protection of this country, particularly against insect-borne diseases and their vectors.

General Simmons suggested that plans for postwar medical research as it affects the Army should be based on the following assumptions: that the security of the Nation depends on the health and physical strength of its people, both military and civilian, and that a continuing program of research on military medicine is essential to this security; that the Army will undertake research of importance to the Army in peace or in war and will share the responsibility but, of course, will not attempt to assume the full burden in those fields common to the military and civilian components of the Nation; that in studying medical problems of significance to the Army full use will be made both of the research facilities within the Army and those made available in certain civilian institutions, the Army directing its attention chiefly to problems which can best be carried out under military conditions; and that the need for medical research by and for the Army bears no direct relation to the size of the Army, since the medical problems of future wars must be anticipated.

Brigadier General Stanhope Bayne-Jones, deputy chief of Preventive Medicine Service, Office of the Surgeon General, described the organization and work of the Board for Investigation and Control of Influenza and Other Epidemic Diseases. It consists of a central board, composed of seven members, and ten commissions, which include about a hundred civilian consultants to the Secretary of War, all of whom are experts in their special fields. These consultants are on a part-time basis and are stationed at their home institutions, but they are called to duty under orders issued through the Office of the Surgeon General. They have worked on more than a hundred projects in Army camps and posts, both in this country and overseas. The plans for postwar medical research now under consideration in the Office of the Surgeon General contemplate not only a continuation of research by the Medical Department itself but also the organization, co-ordination and support of medical research on a national scale.

Dr. A. N. Richards, chairman of the Committee on Medical Research of the Office of Scientific Research and Development, described the work of that committee and brought out the need for some such governmental organization. His committee has discharged its duties through contracts made by the Office of Scientific Research and Development on a "no loss, no gain" basis with colleges, universities, hospitals, research institutions and research groups in commercial companies, as well as through transfer of funds to other agencies of the Government. The contracts cover reimbursements not only for items of equipment, supplies and salaries of assistants but also for salaries of the chief investigators. Nearly five hundred contracts with one hundred and twenty different institutions have been made by this committee, and these involved almost twenty-seven hundred persons, of whom about one fifth were physicians. For the three years ending June 30, 1944, the expenditures for these contracts in successive years amounted to $2,342,440, $5,260,110 and $7,747,276. None of the universities engaged in this work could have undertaken the projects at the expense of their own resources on the scale that the emergency demanded.

The difficulties that Dr. Richards anticipates in developing a peacetime program of this kind are as follows: the vastly broader and more perplexing choice of problems to be studied; the need for a stimulus to replace the ardor for service that imminent national danger has provided, and the need for a type of governmental control so understanding and so flexible that the imagination and scientific passion of investigators will not be dampened; and the increasing difficulties in choosing the institutions to which support shall be given and the definition of the terms with which it shall be offered. He suggested that a thorough survey be undertaken, not only of medical schools and associated hospitals but of the science departments of their universities.

Dr. Lewis H. Weed, chairman of the Division of Medical Sciences, National Research Council, reviewed the work being supported by that council and also described the difficulties that the institutions receiving this aid had experienced in obtaining financial support before the war. He prophesied that in the postwar period it would be even more difficult to obtain the necessary funds. He was convinced that much of medical research will necessarily have to be abandoned in the private and semiprivate institutions of the country unless

governmental subsidies are made available in some form for their support. He thought, however, that any administrative organization created by the Government should take cognizance of the total problem rather than serve merely as a mechanism for handling funds for medical research. It should be an independent agency with broad advisory functions. He added that medical research cannot, in the long run, be divorced from medical schools, from hospitals, from medical practice and from preventive procedures and matters of public health.

Dr. David Heyman, president of the Board of Directors, New York City Public Health Research Institute, described his organization, which he hoped would set a pattern that might be widely followed. This institute is closely associated with the New York City Department of Health but is a completely independent institution. It is governed by its Scientific Council, which initiates and supervises scientific projects, and its Board of Directors, which sets general policies and controls finances. It is financially assisted by the city under a long-term contract but also receives funds from private donors.

Dr. Heyman pointed out the limitations of the various foundations, whose support is necessarily restricted because of their limited resources and because their benefits are spread over a wide field. These foundations usually hope that, when something begins to turn out well, further support will be given by the public and by a governmental agency. He stated that the Government should support medical research by making grants-in-aid to existing nonprofit institutions rather than by setting up new laboratories of its own. In this way, it can provide opportunities for continued service by the many able young scientists now in the armed forces and also provide training for youths who show promise.

From the testimony of these experienced persons, it is obvious that some sort of wide support for medical research must be provided by the federal government if advances in this field are to continue. Incomes from private endowments have dropped off markedly, and the prospects of new funds from similar sources are not particularly good and certainly cannot be expected to keep pace with the growing needs of medical research. During the past decade manufacturers of pharmaceutical and other products have filled some of the gap by generous support of projects in which they have special interests. They have also developed research organizations of their own that are rapidly becoming pre-eminent in the field of medical research. They cannot, however, be expected to carry too much of the burden, which in the long run rightly belongs to all the people, who are the beneficiaries of the results of this research.

THE DOCTOR ILLUSTRATES HIS TRAVEL NOTES

Young Richard Bright, son of a well-to-do Bristol banker and a student in medicine at Edinburgh, went on an expedition to Iceland at the age of twenty-one. With his gifted pen he not only described the botanical and zoological specimens collected by the Mackenzie party, but he also drew some of the illustrations contained in *Mackenzie's Travels in Iceland*, published in 1811. After graduating from Guy's Hospital in 1812, moreover, Bright toured Holland, Belgium and Germany and spent the winter of 1814–1815 in Vienna. His *Travels from Vienna through Lower Hungary*, published in 1818, contains an account of his wanderings and, again, as in the Iceland tour, he drew his own illustrations. Bright's book is perhaps the most worthy of all self-illustrated travel books by a doctor, but many other physicians, both before and after his time, enlivened their accounts with sketches or paintings. Three other examples may be given, two of which are the product of men whose names are household words in medicine.

William Macmichael, also a son of a banker, became a Radcliffe Traveling Fellow from Oxford in 1811. He made several journeys to Russia and Turkey and visited Moscow in 1814 and again in 1817. As a result of the latter trip he published the book *Journey from Moscow to Constantinople in the Years 1817–1818*, which is finely illustrated by drawings of his own.

In 1863 an uprising in Morocco against the Jews came to the attention of the venerable Sir Moses Montefiore. He decided to go to Saffi to advocate,

in person, the cause of his suffering people and set out with a large party, including his physician Thomas Hodgkin. Hodgkin, long curator of the museum and pathologist at Guy's Hospital, had, after he was sixty-five, given up practice and devoted himself to philanthropy. On conclusion of the affair in Morocco, the party went to the Holy Land, and there Hodgkin died, at Jaffa, in 1866. Hodgkin's account of the trip, however, was saved and published the same year under the title *Narrative of a Journey to Morocco in 1863 and 1864*. It is a delightful account, made more so by the excellent drawings of the author. Like Bright and Macmichael, Hodgkin had great ability as an illustrator.

Of slighter scope, but nevertheless of greater interest because of its contemporary nature, is a brief travel diary by the late Harvey Cushing, with illustrations, some in color, by his own hand.[1] Cushing, straight from four strenuous years as a surgical resident under Dr. Halsted at the Johns Hopkins Hospital, visited Le Puy in Auvergne in the summer of 1900, with a Yale classmate. He kept, as was his custom, a diary and to it added numerous sketches revealing, as Dr. John F. Fulton points out in the introduction to the published diary, Cushing's "unusual powers of observation, draftsmanship and humor." Some of the illustrations are water-colors that show remarkable talent. The sketches are characterized by a boldness of line and accurate perspective so notable in the operative drawings that fill his case-records from the time of his house-pupilage at the Massachusetts General Hospital in 1895[2] to the end of his surgical career. This charming account of the holiday visit to Le Puy is a worthy addition to the long list of travel books by doctors and, indeed, is one of the best.

References

1. Cushing, H. *A Visit to Le Puy-en Velay: An illustrated diary*. 40 pp. Cleveland: The Rowfant Club (privately printed), 1944.
2. Viets, H. R. Notes on formative period of neurological surgeon. *Harvey Cushing's Seventieth Birthday Party, April 8, 1939*.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COBB — Albert C. Cobb, M.D., of Marion, died March 21. He was in his seventy-seventh year.

Dr. Cobb received his degree from Albany Medical College in 1892.

A brother and five nephews survive.

LAWRENCE — Charles H. Lawrence, M.D., of Brookline, died March 13. He was in his sixty-third year.

Dr. Lawrence received his degree from Harvard Medical School in 1908. He served as lieutenant in the Army Medical Corps during World War I. In 1922, he was appointed to the Evans Memorial Institute for Clinical Research and became chief of the Endocrine Service there. He served as consulting physician to Jordan Hospital, Plymouth, Choate Memorial Hospital, Woburn, and Sturdy Memorial Hospital, Attleboro. He was physician-in-chief of the Endocrine Clinic at the New England Medical Center and associate professor of medicine at Tufts College Medical School. He was a fellow of the American College of Physicians and the American Medical Association, and a member of the Association for Study of Internal Secretions and the American Clinical and Climatological Association.

His widow, four sons and six grandchildren survive.

NOTICES

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Main Lecture Room of the Harvard Biological Laboratories on Wednesday, April 18, at 8 p.m.

PROGRAM

The Sensitivity of Human Vision to the Spectrum. Dr. G. Wald.

Water and Electrolyte Exchange Between Blood and the Eye. Drs. E. Kinsey and M. Grant.

Composition of Typical Mexican Foods. Dr. R. S. Harris.

ALLERTON HOSPITAL

The next meeting of the Medical Staff of the Allerton Hospital, Brookline, will be held on Thursday, April 19, at 8:30 p.m. Dr. Albert E. Sloane will speak on the subject "Cataract in the Newborn."

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, April 17, at 8 p.m.

Following the business meeting, Drs. V. Everett Kinsey and D. Morton Grant will speak on the subject "Physiology of Aqueous Humor Formation." An informal discussion by Colonel Derrick T. Vail on "Some Aspects of War Ophthalmology" will follow.

NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club of Boston on Friday, April 20, at 8 p.m. Dr. E. Granville Crabtree will speak on the subject "Clinical Data on Some Pelvic and Ureteral Dilatations."

Interested physicians are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 19

FRIDAY, APRIL 20

*9:00–10:00 a.m. Advances in Naval Medicine. Rear Admiral J. J. A. McMullin. Joseph H. Pratt Diagnostic Hospital.

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building, Boston City Hospital.

SATURDAY, APRIL 21

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

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